Chapter 5

Frontal vs. Parietal Involvement in Planning after Cognitive Rehabilitation Therapy of the Dysexecutive Syndrome: Six Case Studies of Stroke Patients.

Introduction

Acquired brain injury can lead to substantial limitations in a person's cognitive and executive functioning and through that limit a person's daily life activities. Especially executive functions (EF) are essential in independent functioning in daily life and after brain injury they are needed even more. This is because EF are involved in a range of adaptive abilities and behaviours and are required most in novel, unstructured, non-routine situations where no external cues are being given, or in situations where the usually performed routine behaviour is no longer useful or appropriate. These kinds of situations are prominent in rehabilitation because then a person finds himself in a new and unstructured life where all previously used routines have to be relearned or compensated for in order to resume previous activities. Therefore, the rehabilitation of executive dysfunctions is essential. Neuropsychological or cognitive rehabilitation therapy (CRT) is recognised as an important factor aiding the process of picking up, as much as possible, life as it was before brain injury (e.g. Carney et al., 2005; Cicerone et al., 2005; Lincoln, 2005). The influence of CRT on recovery of functions after brain injury is studied at different levels to gain more insight in, for instance, therapy effectiveness or recovery prognosis of a specific patient on the function being trained. Progress in functional neuroimaging provides us with the additional opportunity to study the influence of CRT at the level of brain activation. Where EF are concerned, the focus is mainly on processes in the prefrontal lobe. Together with other cortical and subcortical brain structures the prefrontal cortex forms several neuronal circuits which underlie executive functioning. The dysexecutive syndrome can therefore arise irrespective of etiology or location of the lesion. Neuroimaging studies shed light on the processes that underlie recovery of a specific function: restoration of damaged brain areas or activation of new brain areas compensating for the loss of function. There is still relatively little known about the neural processes underlying cognitive and executive functioning in brain-injured patients or the processes responsible for their improvement in functioning after CRT. This study aims to contribute to the reduction of that gap in the knowledge on neuropsychological rehabilitation.

Functional neuroimaging can answer questions which are not easily answered with behavioural studies. To begin with, office based test results do not show the immediate cause of

a specific error or abnormal reaction, thus leaving questions unanswered, such as: why did this subject have a long reaction time, or present with memory complaints although the performance on a memory test was fine? Functional neuroimaging provides insight in underlying processes which eventually can lead to answers on a behavioural level. For instance, intact performance, after brain injury, does not always imply normal neuronal responses. Functional neuroimaging has shown that alternative neuronal and cognitive mechanisms may support the task and mediate recovery (Price, 2002). In some cases, alternative neuronal routes or increased activation in patients offer an explanation as to why they report a task to be more effortful (Cappa, 2003; Cramer, 1997). Furthermore, knowledge of brain regions critical to recovery of function and of the underlying processes of rehabilitation treatments can aid in designing a treatment (Strangman et al., 2005), the decision which treatment to give (Munoz-Cespedes et al., 2005), at which point in the rehabilitation process to start with treatment, and whether or not to give treatment at all in the case of a specific patient (Ricker et al., 2001; Robertson, 2005b). Finally, hard scientific evidence on neuropsychological rehabilitation methods is essential in the pursuit of acceptance and respect for these methods and funding for research on the subject (Robertson, 2005a). Bigler (2003) adds that neuropsychology should keep up with advances like neuroimaging and incorporate them into their practice, as "Neuropsychology is the field that connects neural function to behaviour" (p.615).

Before focussing on the mechanisms underlying recovery in the damaged brain we have to consider how a healthy brain changes in response to experience. Kelly and Garavan (2005) describe three patterns of practice-related activation change: increase, decrease or reorganisation of activation. The patterns found can for instance be explained as a shift from control and attentional areas to task-specific areas or as a shift from one task-specific area to another. Factors that influence which pattern is prominent range from the effect practice has on the cognitive processes underlying the task performance, to the task domain being practiced, the point in practice at which participants are imaged, pre-existing individual differences, and task difficulty.

Similar to changes in healthy brains, experience-dependent neural processes after brain injury have been described to take several forms. Grady and Kapur (1999) propose the following: reorganisation within an existing neuronal network; recruitment of new areas or use of an alternate network; and inclusion of regions surrounding the lesion. There are relatively few neuroimaging studies on the rehabilitation of cognitive and executive functions. The studies that have been conducted have very diverse research designs: dealing with spontaneous recovery or recovery after therapy; and using resting state or activation paradigms. Because there is so little

known in this line of research the results of these differently designed studies must be taken together to serve as a base for new hypotheses.

Recovery after CRT as measured by resting state studies showed an increase of prefrontal blood flow after training of patients with acquired brain injury (Laatsch et al., 1997; Laatsch et al., 1999). These changes were linked to neuropsychological test results and a more active daily life. Activation studies on CRT in patients with schizophrenia led to a similar observation of increased frontal activation (Penades et al., 2002; Wykes et al., 2002). In Wykes' study, three groups were compared: patients receiving CRT focused on EF, patients receiving a control therapy, and a healthy control group. At baseline, patients showed less frontal activation than healthy controls during a working memory test. After therapy the two patient groups showed an increase, while the healthy controls showed a decrease of activation during their second scan. Moreover, marked increases in brain activation in regions associated with working memory were found in those patients who benefited most from the CRT. These differences between patients and healthy controls were also found in a functional neuroimaging study by Sturm et al. (2004) on a training of alertness in stroke patients. Besides improvement on a behavioural level, patients showed increased frontal activation after training, while the control group showed a decrease of frontal activation from the first to the second measurement. In contrast, a number of functional neuroimaging studies comparing activation at baseline of patients who suffered traumatic brain injury with healthy controls have demonstrated that frontal activation in patients was in fact more intense or wide spread during the performance of cognitive or executive function tests (Christodoulou et al., 2001; McAllister et al., 1999; McAllister et al., 2001; Ricker et al., 2001; Scheibel et al., 2003). For normal ageing a comparable effect of increased recruitment of frontal areas has been found (DiGirolamo et al., 2001). An explanation for this similarity between patients with traumatic brain injury and in healthy elderly people could be that they need to recruit more brain areas and use those areas more intensively during the performance of a certain task (Laatsch, Little, & Thulborn, 2004). This altered activation pattern might be the reason why some patients who function well in daily life or have normal test performance complain about cognitive dysfunctioning or report a task to be more effortful. In a study by Laatsch et al. (2004) the authors hypothesize that after CRT subjects might be expected to show a decline in overall activation pattern from the initially excessive activation demonstrated before the treatment began. They explain this by stating that in therapy the subjects are repeatedly confronted with stimuli they find hard to process. As a result

processing would be done more efficiently, which would be evidenced by changes in the activation patterns and improved neuropsychological functioning.

The above shows there are many contrasting findings on the neural processes underlying the recovery of cognitive and executive functions after CRT. Therefore, additional information is needed. We will describe six case studies of stroke patients who had moderate to severe limitations in executive functioning and received CRT (Spikman et al., 2009) aimed at improving this. The focus will primarily be on the changes in brain activation after CRT. We expect that these six subjects will show less frontal activation than healthy controls at baseline. Furthermore, we expect that the subjects who brought therapy to a successful end will show increased frontal activation during the performance of EF tests after therapy. Six months after CRT we expect this frontal activation to have decreased relative to the measurement immediately after CRT as executive functioning is done more effectively. At both measurements after therapy these changes of activation are also compared with performance on neuropsychological tests, and reported changes in every day functioning. As indicated above, it is quite well possible that the change of the pattern of brain activation is more related to subjective changes, e.g. in reported effort, than to changes in test performance.

In summary, with the results of this study we aim to answer the following questions:

- Are stroke patients with impaired executive functions characterised by lower than normal (pre) frontal activation while performing EF tests?
- What is the effect of CRT on the pattern of brain activation while performing EF tests? More specifically: does CRT lead to increased (pre)frontal activation, and how does this change with time after treatment?
- Do the changes in the pattern of brain activation indicated by fMRI parallel changes in neuropsychological test performance and subjective evaluation of everyday functioning and effort?

Methods

Subjects

The subjects taking part in this study were recruited from the group of patients included in a larger study on the effectiveness of a CRT protocol for the treatment of dysexecutive syndrome (Spikman et al., 2009). The main inclusion criteria were: acquired brain injury of a non-progressive nature, with a minimal time post onset of three months and no maximum. Furthermore, patients had to be in the age range of eighteen to seventy and living at home, that

is, they should not be hospitalized or living in a sheltered environment. Possible candidates for the treatment had to be referred for outpatient rehabilitation treatment because of post-injury problems of a clearly dysexecutive nature, either reported by themselves or observed by others. Exclusion criteria were: cognitive comorbidity of such severity that it would impede the patient in following the treatment, severe psychiatric problems and neurodegenerative disorders. Additional exclusion criteria for the fMRI study were: metallic implants, claustrophobia, epilepsy, and pregnancy.

Table 1 *Demographics of subjects*

Subject	Age	Handed	Edu	Injury	Months	CRT
A	62	R	3	ICVA right	6	3
B	56	R	5	ICVA left	21	20
C	75	R	6	ICVA left	9	19
D	55	L	4	ICVA left	7	20
E	58	R	6	ICVA right and HCVA right	5	24
F	59	R	2	ICVA vertebral-basilar	6	16

Age = age at time of stroke; Edu = educational level (determined using the seven point scale of Verhage (1964) which runs from less than six years primary school (1) to university level (7)); Months = number of months between stroke and start of CRT; CRT = number of sessions

Six subjects (table 1) participated in the fMRI study. They were all referred for CRT following stroke. Specific lesion information can be found in the results section where results are described for each subject individually. Reasons for referral were low scores on executive functioning tests, subjects reporting executive functioning problems in daily life, and partners of subjects reporting them to have executive functioning problems. In most subjects at least two of these reasons were applicable. Time since stroke ranged from five to twenty-one months, with a mean of nine months. The purpose and risks of the study were explained to the subjects, who gave written informed consent to participate. The ethical review board of the University Medical Center Groningen approved of the study.

Therapy

Patients were treated with a newly designed protocol: 'Multifaceted Treatment of the Dysexecutive Syndrome' (Spikman et al., 2009). In this protocol patients learn to cope with a broad range of goal setting-, planning- and regulation problems, with the final aim to improve everyday functioning. The specific skills and strategies chosen to focus on are individually tailored to the patient's particular problems, needs and goals. The protocol consists of three modules: Information and Awareness; Goal setting and Planning; and Initiative, Regulation and Problem solving. For five subjects the number of one-hour CRT sessions ranged from sixteen to

twenty-four, with a mean of nearly twenty sessions and spread over a period of three months. The total number of sessions was determined by a subject's progress in therapy. One patient decided after the third session that he did not want to continue the CRT, but he agreed to return for the second and third measurements thus providing data on repeated measurements without CRT. Further details on the therapy are given in Spikman et al. (2009).

Measures and Procedures

Neuropsychological tests and questionnaires

All subjects underwent neuropsychological testing and had to fill in questionnaires at three points in time. Also a proxy was asked to fill in questionnaires each measurement. First or baseline measurement (T0) was performed before starting the first therapy session. The second testing (T1) was completed directly after ending therapy and follow-up testing (T2) was done four to seven months after ending therapy. Neuropsychological assessment was done by a trained examiner.

The neuropsychological measures used, were based on a study conducted in the same outpatient rehabilitation population. In this study measures were determined which successfully discriminate between brain-injured and non-brain-injured subjects (Boelen et al., 2008). A selection of subtests was used from the Behavioural Assessment of the Dysexecutive Syndrome (BADS; Wilson et al., 1996) in its Dutch translation (Krabbendam et al., 1997): the Key Search Test raw score (KS), the Modified Six Elements Test total raw score (MSET), and the Zoo Map Test total raw score (ZOO). Of this last subtest a parallel version was used during T1 (Spikman et al., 2000b). In the Twenty Question Test (Laine & Butters, 1982) subjects are asked to guess which of 42 drawings of objects representing overlapping classes such as animals, clothing, or round objects, the examiner has in mind. The subject is instructed to do this by asking the examiner questions to which the examiner can only answer "yes" or "no". A maximum of twenty questions is allowed. Several scores of the Tower of London (ToL; Shallice, 1982) were added because subjects were also asked to do this test inside the scanner: number of items correct in one trial, total number of items correct, and total time. At T2, a newly designed test was administered in addition to these existing neuropsychological tests: the Executive Secretariat Task (Spikman et al., 2007), which is considered a more ecological valid measure of executive functioning (Lamberts, Evans & Spikman, 2009a). The test yields three scores: Initiative, reflecting all the actions the subject has initiated without being instructed; Prospective, reflecting all the actions that were correctly carried out on a later moment; and Executive, reflecting all the actions that were correctly carried out at all. Together these scores form the

total score. Besides these neuropsychological tests, the Dysexecutive Questionnaire (DEX; Burgess et al., 1996), both patient and proxy, and the Role Resumption List (Spikman et al., 2003) were administered. The Role Resumption List is a structured interview which indicates the extent to which a subject feels he or she has returned to the same level of activities in daily life as before brain injury. Finally, the achievement of the goals the subjects set for themselves during CRT was determined through a checklist. To correct for possible test-retest effects we used control group data from the related study by Spikman et al. (2009).

fMRI tests

Scanning was also done three times and was always planned as close to the neuropsychological testing session as possible. Magnetic Resonance Images were acquired on a Philips Intera 3.0 Tesla MR system equipped with an eight channel sense head coil at the Neuroimaging Center Groningen. Anatomic imaging was performed with a whole-brain T1 weighted sequence (TR, 25 ms; TE, 4.6 ms; flip angle, 30°; matrix, 256 × 256; field of view, 256 mm; slice thickness, 1 mm; number of slices, 160). Functional images were acquired with a echoplanar imaging sequence (TR, 3000 ms; TE, 35 ms; flip angle, 90°; matrix, 64 × 64; field of view, 224 mm; slice thickness, 3.5 mm; number of slices, 46). The total number of volumes differed in the two tests the subjects were presented with, but always ranged from 300 to 315.

Subjects were asked to perform either one or two tests in the fMRI scanner. All six subjects were presented with the Tower of London (ToL). Within the course of our study we developed a new test: the Daily Life Planning test (DLP; Lamberts, Renken, Brouwer & Spikman 2009b). As the subjects were trained in contextually rich activities we felt the ToL was too abstract and artificial to measure the effect of CRT. Therefore we developed a test that, like the ToL, involved subgoaling, but also involved elements from real planning situations in daily life. The three last subjects included were additionally presented with the DLP in the scanner. Stimuli were projected on a screen behind the scanner. Subjects could see these stimuli via a mirror above their head. For both tests a block design was created in which an active condition (60 s) alternated with a control condition (60 s). There were ten blocks in total. Prior to the first and after each block there was a rest period (30 s) in which the subject was instructed to focus on a cross in the middle of the screen. These rest periods were included to make the scanning period less exhaustive for the subjects. Both the active and the control condition were self-paced, but turned automatically to the rest state after one minute regardless of whether the subject had responded to the current trial. Each block, including rest, started with an instruction that was

displayed for three seconds. In both the active and the control conditions four possible answers were presented at the bottom of the screen. The location of the answers on the screen corresponded to the buttons on two response boxes, which the subject held in left and right hand. The subject could respond by pressing one of four buttons. The specific test items were randomised for each subject. Prior to the fMRI experiment the tests were explained and practiced.

During functional measurement, behavioural data (scores on the tests) were collected as well. Imaging data were analysed using SPM2. Functional data were realigned, normalized and smoothed using Gaussian kernel with a full width of half maximum of 7 mm. Voxels with a signal increase during the active condition in comparison to the control condition were labelled as positively activated. In individual analysis, active voxels were identified by applying a threshold to the T-maps ($p<0.05$ family wise error correction, $T>3.00$). For each of the three scanning sessions, we calculated the increases or decreases of activation in a specific area from one session relative to another. In group analysis, no correction was used ($p < 0.02$, $T>2.76$). In individual analysis, T-maps were projected on subjects' own anatomic images. In group analysis, the T-maps were projected on an anatomical template using MRIcro (http://www.sph.sc.edu/comd/rorden/overlay.html). Group analysis was done for all six subjects at T0. At T1 and T2 subject A, who did not complete CRT, was excluded from group analysis.

Tower of London As stated above we feared that generalization from the real life planning situations in CRT to a test like the ToL was likely to be problematic. However, we included the ToL because our aim was to evaluate a training focused at planning and goal management and it is a typical subgoaling paradigm which has been used very often in fMRI. The original ToL was adapted for fMRI use. We combined the designs of two previous neuroimaging studies on the ToL (Lazeron et al., 2000; Newman et al., 2003). In the active condition subjects were presented with a start and a goal position on a single screen (figure 1) (after: Lazeron et al., 2000). Each configuration consisted of three balls of different colours (red, green and blue) placed on rods of different heights. The left most rod could hold three balls, the middle two balls and the right rod only one ball. Subjects were asked to plan internally the minimum number of moves needed to reach the goal position from the start position, with the restrictions that only one ball at a time could be moved and only when there was no ball on top. Possible answers were: one or two, three, four, and five or more moves (after: Newman et al., 2003). In the control condition subjects were presented with the same two configurations, but this time were asked to add up the number of red and blue balls displayed. In this condition there were six balls on the screen

and the number of red and blue balls differed in each new trial. Again, the possible answers were: one or two, three, four, and five or more.

Daily Life Planning test. This test was designed as an ecologically valid parallel version of the ToL: it involved planning steps towards a final goal, but the goals in the DLP could also have appeared in daily-life. Other studies demonstrated successful use, in a brain-injured population, of a test in which steps had to be planned towards a real-life goal (Cazalis et al., 2001; Dritschel et al., 1998). In both studies differentiation between healthy controls and patients was possible and in Cazalis' study the patients' performance was significantly correlated with behavioral modifications in everyday life. Very recently, a similar task which involved subjects ordering events from daily-life activities was successfully used in an fMRI study (Krueger et al., 2007). The DLP consisted of fifteen scripts, each of which described the steps towards a different daily-life goal (table 2). For each subject, five scripts were randomly selected from the group of fifteen; in each block one script was presented. Four steps, randomly selected from the total number of steps (12-25) towards a goal, were displayed on a single screen (figure 2). On every trial subjects were asked to decide which of these steps would be the first to take in order to reach the goal.

Table 2 *Fifteen scripts used in the DLP and the number of steps towards a goal described in each script.*

Script	**Number of steps**
Preparing potatoes for diner	12
Going to the cinema	12
Organizing a party	12
Making coffee	12
Making a phone call	12
Shopping for groceries	16
Learning a language	16
Going to work	16
Going to the bank	16
Looking for a job	16
Celebrating your birthday	16
Starting a brokers office	20
Travelling by train	20
Booking a holiday	20
Renovating a house	25

Subjects did not have to keep track of decisions made earlier. In the control condition subjects were presented with four sentences of equal length as the sentences in the active condition. All four sentences had to be read before choosing the sentence in which nonsense was written. Correct sentences were for instance: "Having a conversation with your neighbour" or "I love playing the piano". Nonsense sentences were: "Tomorrow the weather will be green" or "The

rabbit phoned the queen". In three trials, spread over the five blocks of the control condition, two instead of one nonsense sentence was presented. During instruction subjects were told this might happen every now and then, but were not told when or how often it could occur.

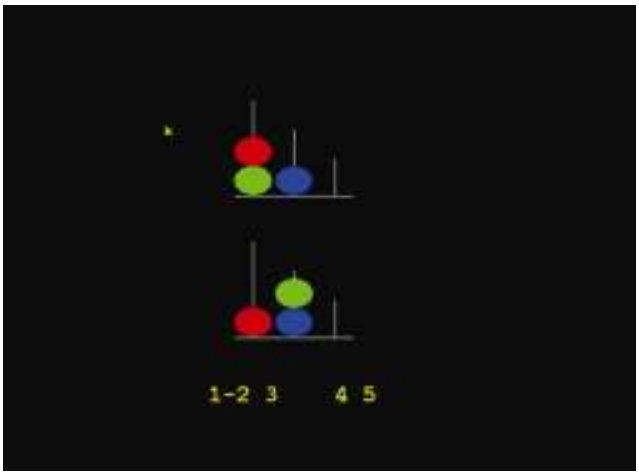

Figure 1. Example of the ToL screen. This display shows a three move problem. The start state is presented above the goal state. The participant has to decide how many moves it takes to the reach the goal state from the start state. The four possible answers are presented at the bottom of the screen. The placing of these answers on the screen corresponds to the four buttons on the response boxes which the participant holds in left and right hand.

Figure 2. Example of the DLP screen. The participant is asked to decide which step to take first when the goal is 'going to the bank'. The four alternatives are presented at the bottom of the screen. The placing of these possible answers on the screen corresponds to the four buttons on the response boxes which the participant holds in left and right hand. (Translation of the steps: presenting the form to the bank clerk, thanking the bank clerk, it is your turn to go to the counter, signing the transaction form)

If they found two sentences could be nonsense, they were instructed to choose that sentence that appeared most illogical to them. This ensured subjects read all four sentences before

making a decision, similar to the active condition. In summary, in both the active and control condition subjects had to read four short sentences, think about the content of the sentence, make a decision, and press a button. The only difference was that in the active condition the decision involved planning. This difference was exactly what we were interested in.

Results

Brain activation patterns during the ToL analysed for the group as a whole (figure 3) showed the least frontal activation at T1. In contrast, the parietal lobe showed the highest level of activation at that measurement. The activation pattern at T2 was comparable to that at T0, but at T2 this activation was more intense and wider spread.

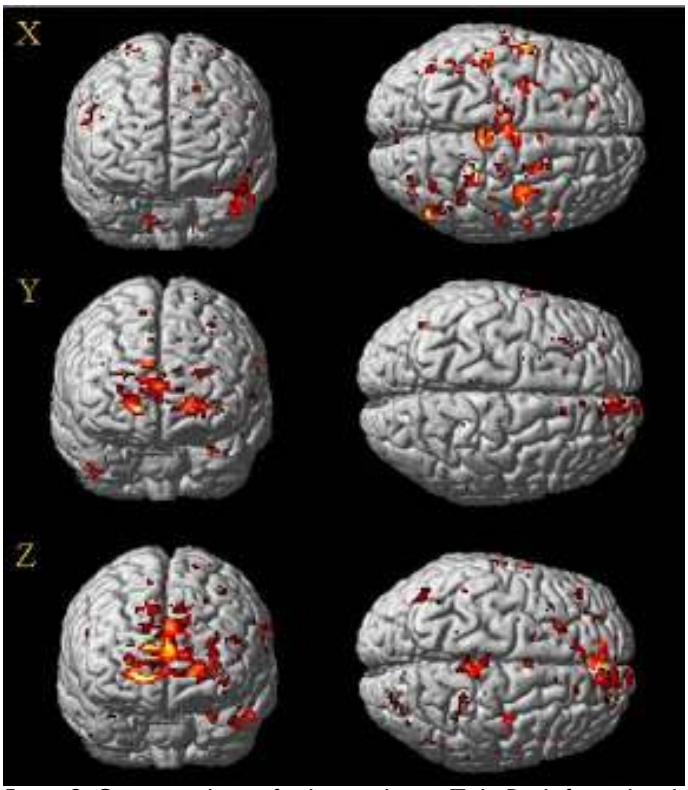

Figure 3. Group analysis of subjects during ToL. Both frontal and top view of the brain are shown. X= stronger activation at T1 compared to T0, Y= stronger activation at T2 compared to T1, and Z= stronger activation at T2 compared to T0.

With only three subjects, group analysis of the DLP was hardly possible. It did not result in a clear activation pattern, but in activation spread throughout the brain, especially at T1. At T2 there was a little less pronounced activation relative to T1, but more activation than during T0.

For both tests, no relationship was found between brain activation and scores on the tests performed in fMRI. Brain activation during both tests was also analysed per subject (tables 3, 4 and 5). These data are presented below.

Additionally, there are results on the neuropsychological tests and questionnaires. As expected, performance on neuropsychological tests did not show a clear trend of either improvement or worsening after therapy. The Executive Secretariat Task was more informative in that performance on this test reflected reports of the subjects and/or their partners on problems they encountered in daily life. On the Role Resumption List three subjects reported that daily life was again a little more like it used to be before stroke at every next measurement, two subjects reported an increase of daily life activities at T1 and at T2 a decrease, and one reported no change in daily life activities. Surprisingly, three subjects reported an increase of problems at T2 relative to T0 on the DEX. Two others reported an increase of problems from T1 to T2. Subjects and their partners do not always seem to agree on the amount of problems experienced in daily life, but also in the case of the DEX-proxy the majority reported an increase of problems either at T1 or T2. Also these results will be discussed for each subject separately.

Subjects presented with ToL only

Subject A

This subject was right-handed, had educational level three, and suffered an ischaemic stroke high in the right internal carotid artery at the age of 62. Beforehand he had several transient ischaemic attacks in the same area. CT-scan during admission in hospital showed that a large area at that site had been affected. He was referred for treatment of the dysexecutive syndrome six months post-onset. Anatomical MRI at T0 showed: several white matter lesions both left and right and shrinkage of the right caudate nucleus head. After three sessions he decided to stop therapy, but was willing to further undergo neuropsychological testing and fMRI scanning at the same time schedule as the other subjects, thus providing data on repeated measurements without therapy. No therapy goals were formulated.

fMRI data showed that at T1, as compared to T0, this subject showed stronger activation in the left medial and left inferior frontal lobes, and the left precuneus. Furthermore, a decrease of activation was found in the left superior frontal lobe and the right inferior parietal lobe. At T2 the only increase relative to T1 was found in the right superior frontal lobe. Most

areas showed a decrease of activation: the left middle and right inferior frontal lobe, and the inferior parietal lobe bilateral. In comparison to T0 all frontal activation during T2 was less.

He performed well on the Executive Secretariat Task with only a slightly low score on the prospective subscale. On the DEX subject A reported an improvement at T1 and a little worsening at T2. His wife reported a lot more problems at T1 and even a bit more at T2. At T1 he reported that his daily life activities had changed more to what they used to be like before the stroke, but at T2 there was a decrease of activity level again.

In summary, compared to T0 there was mainly an increase of frontal activation at T1, while at T2 there was mainly a decrease. The precuneus showed an increased activation in the left hemisphere at T1, while the parietal inferior lobe showed a decrease of activation at T1 and even further decrease at T2. He performed well on the Executive Secretariat Task and reported improvement of executive functioning and daily life functioning at T1, but a little worsening at T2. His wife reported worsening at T1 and further worsening at T2.

Subject B

This subject suffered a mild ischaemic stroke in the left hemisphere three days after his 56th birthday. As a result he had word finding problems, minor loss of motor functioning in his right hand and cognitive complaints. He was right-handed, his educational level was five, and he started therapy twenty-one months post onset. MRI at T0 showed a cortical lesion in the left parietal lobe. In total he had twenty one-hour sessions. He set the following goals for himself to achieve through therapy: increasing initiative, finishing what has been started, realistic time management, and above all being more satisfied with his regained abilities.

fMRI at T1 relative to T0 showed a decrease of activation in the left superior and right medial frontal lobes, and the right precuneus. Compared to T1, at T2 frontal activation increased again: right superior, bilateral medial, and left inferior frontal lobes were activated stronger. Activation in the left inferior parietal lobe decreased relative to T1. Comparing T2 with T0, there were no differences in parietal activation; stronger activation in the right superior and left inferior frontal lobes at T2; and stronger activation in the right medial and right inferior frontal lobes at T0.

His scores on the Executive Secretariat Task were all very low except for his score on the prospective subscale. On the DEX, the subject reported more problems at each next testing session. His wife reported an increase of problems at T1 and a decrease again at T2 only two

points below T0. At each consecutive testing session he found that his daily life had become a little more like it used to be before stroke. The only goal which he, according to himself, really had achieved at T2 was realistic time management.

In summary, fMRI data at T1 showed a decrease of frontal and precuneus activation as compared to T0. At T2 relative to T1 frontal activation increased again and left inferior parietal lobe decreased. Subject B had low scores on the Executive Secretariat Task, reported an increase of problems experienced at each consecutive measurement, and felt he had only achieved one goal he had set for himself during therapy. In contrast, he experienced his daily life becoming more and more the same as before the stroke. His wife reported more executive functioning problems at T1 relative to T0 and a decrease of problems at T2 below both T0 and T1.

Subject C

Subject C was right-handed, had educational level six, and was 75 years old when he suffered an ischaemic stroke in the left middle cerebral artery affecting the temporal lobe. Six months prior to the stroke he was already diagnosed with atrial fibrillation and treated for it. Next to cognitive and motor problems he had aphasia. After clinical language therapy he was able to understand and produce spoken and written language. However, he was still impaired in all those language functions. Nine months after his stroke he was referred for CRT aimed at executive functioning. MRI at T0 showed a cortical lesion from the left temporal lobe to the angular gyrus. Due to his high age he was excluded from the larger study by Spikman et al. (2009), but he was included in the neuroimaging study and had nineteen therapy sessions. His goals for therapy were: achieving goals in daily life without being distracted and managing large amounts of information when being overwhelmed by it.

At T1 compared to T0, there was an increase of frontal activation in the left superior and left medial lobe and a decrease in the left inferior lobe. At T2, activation in the right superior frontal lobe decreased in comparison to T1. Activation of the right precuneus increased at T1 relative to T0, and at T2 the right inferior parietal lobe showed increased activation as compared to T1. Comparing activation at T0 with T2 showed right superior, left inferior and left orbitofrontal lobes were stronger activated at T0, while the left medial frontal lobe was stronger activated at T2. The left inferior parietal lobe was stronger activated at T0 than T2, while its right counterpart was stronger activated at T2.

His performance on the initiative subscale of Executive Secretariat Task was poor, but he performed well on the other three subscales. On the DEX he reported no change in executive problems at T1, but an increase of problems at T2. His partner reported at T0 and T2 to experience almost the same amount of problems; a little more at T2. The goals he had set had partly been reached. The subject found he was better able to manage distraction, but still found it hard to manage information, especially when it was spoken or written information. He decided to try and accept that and left situations in which information had to be handled over to his son or partner. In daily life the most obvious change was that he started driving again. At T2 he stated that, compared to T0, he was less satisfied with the way he could participate in daily life activities.

In summary, at T1 relative to T0 increases of activation were found in two frontal areas and a decrease in one. At T2 there was a decrease of frontal activation as compared to T1. Most frontal areas showed stronger activation at T0 than at T2. In the parietal lobe there were increases at T1 and T2. His Executive Secretariat Task scores were fine except for his score on the initiative subscale. He experienced most problems and was less satisfied with his daily life activities at T2. His partner did not report a change in executive functioning problems.

Subjects presented with ToL and DLP

Subject D

This subject was left-handed and his educational level was four. At age 55 he suffered a severe ischaemic stroke in the left middle cerebral artery area. Sulci in this area seemed affected. Thrombolysis resulted in rapid improvement of motor function, but aphasia remained. During clinical language therapy, the subject improved and at the time he was referred for CRT he had slight word finding problems, was a little slower in formulating sentences and needed a little more time to process spoken or written information. Understanding of instructions went well. Seven months post onset he started therapy and he had twenty sessions in total. MRI at T0 showed left fronto-parietal atrophy with wide sulci, including the Sylvian fissure, and white matter lesion below the left angular gyrus. During therapy he formulated two goals for himself: in preparation of an activity think ahead of the steps needed to be taken, and keeping better track of the time spent at a certain activity.

At T1 all frontal activation found was stronger compared to T0 activation in both the ToL and the DLP. In the ToL the activation was stronger in the left superior, right medial, left inferior and bilateral orbitofrontal lobes. During the DLP, activation was stronger bilaterally in the medial, inferior and orbitofrontal lobes. Also parietal activation increased from the T0 to T1: in the left precuneus and bilateral inferior parietal lobe during the ToL and in the right inferior parietal lobe during the DLP. At T2 compared to T1, during the ToL, there was again an increase of a few frontal areas, all in the left hemisphere: superior, medial and inferior lobes. In contrast, in the DLP there was a decrease of left frontal medial activation. Inferior parietal lobe activation showed an opposite pattern: a decrease bilaterally during the ToL and an increase in the left hemisphere during the DLP. In general, both frontal and parietal activation was stronger at T2 thanT0.

The Executive Secretariat Task scores of subject D were fine with only the score on the executive subscale being slightly low. On the prospective subscale he had the maximum score. On the DEX he reported a lot less problems at T1 and again a lot more at T2. His wife had the same experience although she reported a smaller difference between the measurements. At T1 and T2 he was more satisfied with the way he could participate in daily life activities than he was before therapy. According to him he had completely achieved his goals for the therapy, already at T1.

Summarised, at T1 there was a significant increase of both frontal and parietal activation. At T2 frontal activation increased further during the ToL, but decreased in the left medial frontal lobe during the DLP. Parietal activation decreased during the ToL and increased during the DLP. He performed well on almost all subscales of the Executive Secretariat Task. Subject D experienced fewer problems at T1 and more at T2 as did his wife, but was satisfied with his functioning in daily life.

Subject E

This subject was right-handed and had educational level six. A few weeks before his 59th birthday he had an ischaemic stroke in the right middle cerebral artery area. After thrombolysis he had a hemorrhagic stroke also in the right hemisphere. During that hospital admission the subject was also diagnosed with atrial fibrillation. Five months after his stroke he started CRT. At T0 MRI showed a right lateral-frontal lesion including the frontal operculum. He formulated five goals for himself: controlling emotions, driving, making decisions on how to fill in his

professional career, managing the scarce amount of energy, slow down speed of acting to be inline with his slowness of thinking so fewer mistakes will be made.

At T1 compared to T0 the left superior and left medial frontal lobes showed a decrease of activation, while the right inferior frontal lobe is activated stronger during the ToL. In contrast, during the DLP, the left superior frontal lobe showed stronger activation and the left inferior frontal lobe showed weaker activation at T1. In the parietal lobe the only difference is found during the DLP where, at T1, the right precuneus showed a decrease in activation and the right inferior lobe an increase relative to T0. At T2 there is no difference in intensity of activation found during the DLP when compared to T1. In the ToL however, the right orbitofrontal and left superior frontal lobe showed increased activity, while the right medial and right inferior frontal lobes showed a decrease. Comparing T2 with T0 during the ToL, some frontal areas were stronger activated, while other showed less activation. During the DLP there was more frontal activation at T2.

On the Executive Secretariat Task he scored very well on each subscale, suggesting good executive functioning in daily life. This subject reported an increase of problems in executive functioning at T1. At T2 he experienced a decrease, but there were still more problems than at T0. His wife reported most problems at T2. His daily life activity level was a little more like it used to be before stroke at each consecutive measurement. At T1 he claimed to have achieved his goals a great deal and at T2 all goals but one were completely achieved. Only the control of his emotions was not yet fully achieved according to himself.

Summarised, at T1 most frontal areas showed a decrease in activation compared to T0. At T2 the DLP showed no difference in activation and the ToL resulted both in frontal increases and decreases. The Executive Secretariat Task went very well. At T0 this subject reported the least executive problems and at T1 the most. His wife reported most problems at T2. His daily life activity level had become more like it used to be and all goals, but one, had been achieved.

Subject F

At age 59 this right-handed subject suffered a vertebral-basilar ischaemia. There were no signs of an infarct at MRI scans. Educational level of this subject was two. Six months after his stroke he was referred for CRT, and had sixteen sessions in total. At T0 there were no lesions visible on MRI scans. As goals for therapy he formulated: more peace in my head, daily life more organised, stop impulsiveness, keeping track of time during an activity.

Comparison of frontal activation at T0 and T1 in both the ToL and the DLP showed most areas were stronger activated at T0. At T0, activation is stronger in the left superior, left inferior, and bilateral orbitofrontal lobes during the ToL; and in the left superior, right medial and bilateral inferior frontal lobes during the DLP. At the same time activation during the ToL is weaker in the right superior and right medial frontal lobes, and during the DLP in the orbitofrontal lobe bilaterally. The right inferior parietal lobe showed an increase in activation at T1 compared to T0 during the ToL, while there was a decrease of precuneus and inferior parietal lobe activation during the DLP. At T2 most frontal areas showed an increase of activation relative to T1. During the ToL the right superior, left medial, bilateral inferior, and left orbitofrontal lobes were stronger activated, while the right orbitofrontal lobe was activated weaker. During the DLP, bilateral superior, right medial, and bilateral inferior frontal lobes were stronger activated; and the left medial frontal lobe was activated weaker. In the parietal lobe there were decreases in activation in the precuneus and inferior lobe during the DLP. During the ToL the precuneus showed a decrease, while the right inferior parietal lobe showed an increase of activation. In general, more frontal areas showed increased activation when comparing T2 with T0.

On the Executive Secretariat Task this subject performed poorly on all subscales, his best score was on the prospective subscale. Unfortunately, the DEX was not presented to this subject and his wife at T1. Therefore we can only present scores at T0 and T2. Both partners reported most executive functioning problems at T0. According to the subject his daily life was a little more like before he had the stroke at each consecutive measurement. At T2 the subject reported most goals to be almost or completely achieved, with the exception of his desire to control his impulsiveness which, to his opinion, was only a little under control.

In summary, in the DLP the strength of frontal and parietal activation mostly decreased from T0 to T1. At T2 parietal activation further decreased, while most frontal areas showed an increase of activation. The main pattern in the ToL was a decrease of activation in frontal areas and an increase of parietal activation at T1. At T2 there was an increase frontally. Subject F had low scores on the Executive Secretariat Task. Both the subject and his wife reported a decrease of executive functioning problems at T2. The subject experienced his daily life activity level to have changed towards the level it used to be and he found he had achieved the therapy goals except for the goal on impulsiveness.

Table 3 *Areas with significant increases of activation during the ToL.*
First, increased activation at T1 relative to T0 is presented, then at T2 relative to T1, and finally increases at T2 relative to T0.
L = left hemispheric activation, R = right hemispheric activation

Active area	**Brodmann**	**T1>T0**						**T2>T1**						**T2>T0**					
		Subjects																	
		A	**B**	**C**	**D**	**E**	**F**	**A**	**B**	**C**	**D**	**E**	**F**	**A**	**B**	**C**	**D**	**E**	**F**
Orbital gyri	11, 12, 47				LR							R	L				L	R	L
Superior frontal gyrus	8, 9, 10, 11, 12			L	L		R	R	R		L	L	R		R		LR	R	R
Middle frontal gyrus	8, 9, 10, 11, 12, 46	L		L	R		R		LR		L		L			L	LR		L
Inferior frontal gyrus	44, 45, 47	L			L	R			L		L		LR		L		LR	L	L
Precuneus	7	L		R	L														
Superior parietal lobule	5, 7								L								L		
Inferior parietal lobule, supramarginal and angular gyri	39, 40				LR		R			R			R	R		R	LR		R

Table 4 *Areas with significant decreases of activation during the ToL.*
First decreased activation at T1 relative to T0 is presented, then at T2 relative to T1, and finally decreases at T2 relative to T0.
L = left hemispheric activation, R = right hemispheric activation

Active area	**Brodmann**	**T1<T0**						**T2<T1**						**T2<T0**					
		Subjects																	
		A	**B**	**C**	**D**	**E**	**F**	**A**	**B**	**C**	**D**	**E**	**F**	**A**	**B**	**C**	**D**	**E**	**F**
Orbitofrontal gyri	11, 12, 47	L					LR						R	L		L			R
Superior frontal gyrus	8, 9, 10, 11, 12		L			L	L			R				LR		R			
Middle frontal gyrus	8, 9, 10, 11, 12, 46		R			L		L				R		R	R			LR	
Inferior frontal gyrus	44, 45, 47			L			L	R				R		LR	R	L		R	
Precuneus	7		R										L						
Superior parietal lobule	5, 7							L											
Inferior parietal lobule, supramarginal and angular gyri	39, 40	R						LR	L		LR			L		L		R	L

Table 5 *Areas with significant increases and decreases of activation during the DLP.*
First activation at T1 relative to T0 is presented, then at T2 relative to T1, and finally T2 relative to T0.
L = left hemispheric activation, R = right hemispheric activation

Active area	**Brodmann**	**T1> T0**			**T1<T0**			**T2>T1**			**T2<T1**			**T2>T0**			**T2<T0**		
		Subjects																	
		D	**E**	**F**	**D**	**E**	**F**	**D**	**E**	**F**	**D**	**E**	**F**	**D**	**E**	**F**	**D**	**E**	**F**
Orbital gyri	11, 12, 47	LR		LR										L		L			
Superior frontal gyrus	8, 9, 10, 11, 12		L				L			LR				R	R				L
Middle frontal gyrus	8, 9, 10, 11, 12, 46	LR					R			R	L		L	L	R				
Inferior frontal gyrus	44, 45, 47	LR				L	LR			LR						L			
Precuneus	7					R	R						LR					LR	
Superior parietal lobule	5, 7	R											R	R					
Inferior parietal lobule, supramarginal and angular gyri	39, 40	R	R				L	L					R	L					

Discussion

Brain activation patterns were analysed for the total group of patients who successfully completed therapy as well as for each subject separately. The last method was recommended in order to make valid clinical interpretations when analysing imaging data of brain injured subjects (e.g. Bigler, 2001; Hillary et al., 2002). The wide variability in anatomical and functional organisation after brain injury complicates the interpretation of data. Recovery of function or intact task performance may be the result of several, individually variable, neuronal and cognitive mechanisms (Price, 2002; Weiller, 1998). Furthermore, the question whether the lesion has displaced or replaced the healthy tissue surrounding it makes spatial normalisation difficult (Hillary et al., 2002).

However, there were interesting trends in activation patterns found in the group as a whole. Compared to a group of healthy subjects presented with the same tests (Lamberts et al., 2009b, the group of patients in the present study showed less frontal and more parietal activation at all three measurements. This lower level of frontal activation in patients at T0 is in line with what we expected to find and was not caused by focal frontal lesions as all of them had lesions elsewhere in the brain. Their dysexecutive syndrome, and the lower level of frontal activation, was a result of diffuse damage to other structures part of the neuronal network underlying executive functioning. The stronger frontal activation in the healthy control group performing the ToL (figure 4) was mainly localised in the right frontal lobe. During the DLP the healthy control group showed stronger activation in the dorsolateral prefrontal cortex and the anterior cingulate cortex, with slightly more activation in the left hemisphere. Regarding the DLP, we should be careful drawing conclusions as only a small number of subjects performed this test in the present study. However, as results on both tests are similar, we can conclude that brain injured subjects relied more heavily on parietal areas while performing EF tests than healthy controls, whereas the latter showed stronger activation in frontal areas associated with EF.

This increased parietal activation in the brain injured subjects (figure 5) was surprising. It was expected to find activation in the parietal lobe as this has been found in a number of studies using the ToL (e.g. Baker et al., 1996; Heuvel van den et al., 2003; Lazeron et al., 2000). However, we did not expect the parietal lobe to play as large a role as it did. A probable cause of this parietal hyperactivity might be found in the low level of frontal activation. In the study by Van den Heuvel et al. (2003) an fMRI paradigm with the ToL was used which was very similar to ours. They focused on the effect of task complexity in a group of healthy subjects. Next to

frontal brain areas, they found the bilateral precuneus and inferior parietal cortex to be correlated with increased task load. These parietal areas therefore seem to be involved in the actual planning component of the test and not mainly in visuo-spatial information processing as suggested by earlier studies using the ToL (Baker et al., 1996; Dagher et al., 1999). Also other authors have discussed the involvement of parietal areas in executive functioning (e.g. Cavanna et al., 2006; Fassbender et al., 2004; Szameitat et al., 2002).

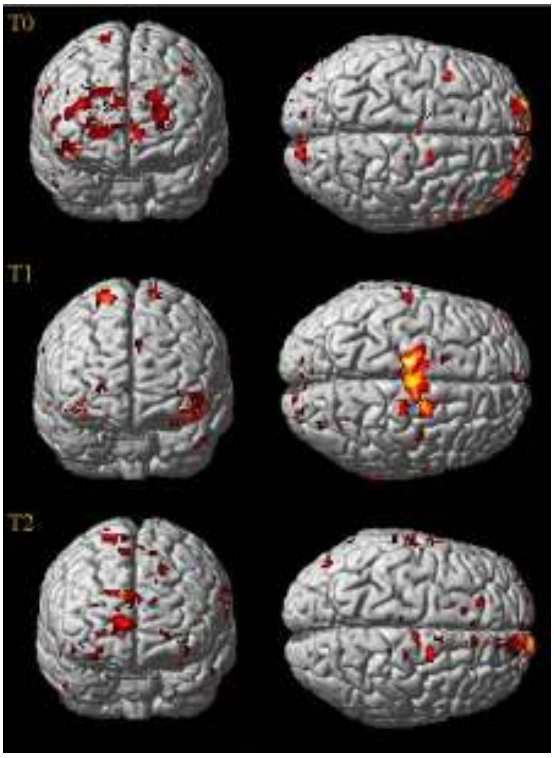

Figure 4. Group analysis while performing the ToL; stronger activation of sixteen healthy controls (Lamberts et al., 2009b) compared to the stroke subjects. Activation patterns were compared at T0, T1 and T2. Both frontal and top views of the brain are shown.

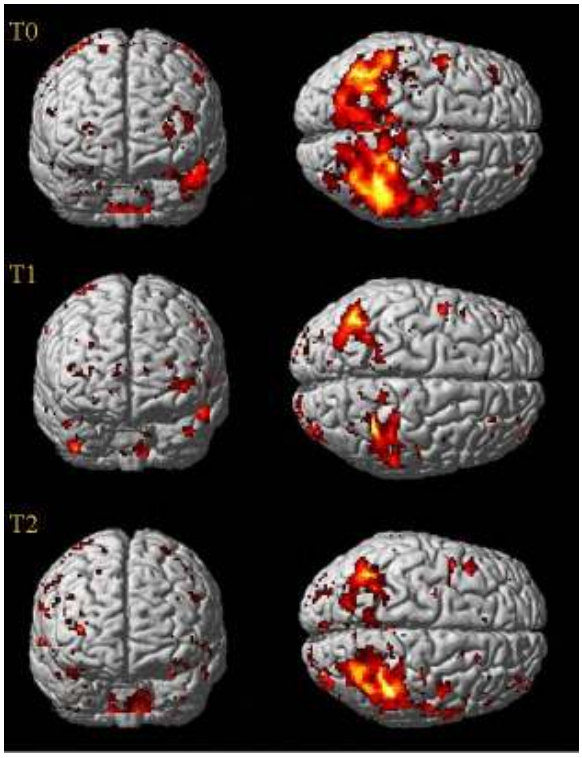

Figure 5. Group analysis while performing the ToL; stronger activation of the stroke patients compared to sixteen healthy controls (Lamberts et al., 2009b) . Activation patterns were compared at T0, T1 and T2.
Both frontal and top views of the brain are shown.

There is of course also an explanation more in line with the visuo-spatial information processing role of the parietal lobe. Subjects presented with a complex ToL problem or subjects suffering a dysexecutive syndrome might recruit their visual-processing system more because they have to

scan the visual information more often and have more difficulty to keep track of the steps they have already taken to reach the solution. Either way, in our subjects, it could well be that to compensate for hypofrontality the parietal lobe was recruited and that six months after CRT hypofrontality had not recovered sufficiently so parietal compensatory activation was still needed. This brings us to the unexpected results concerning the frontal lobe activity. We did not find a direct increase of frontal activation after CRT. Nor did we find a relative decrease of frontal activation at T2 compared to T1; we found an increase. We expected that at T2 executive functioning would be performed more efficiently and less dependent on strict control by frontal processes. Our results suggest that in many cases there is a more delayed increase of frontal activation, a while after CRT has ended. As this frontal increase was accompanied by a parietal decrease in activation it further strengthens our parietal compensation hypothesis. Interesting questions for further research on this point would be whether frontal activation further increases and parietal activation further decreases over time. Furthermore, the exact function of the extra parietal activation should be studied. Is it involved in the planning process or is it a result of more intense visuo-spatial information processing?

fMRI data were also considered in combination with the results on measures of executive functioning in daily life. These measures answered the most important question for the participating subjects: did they improve in executive functioning after CRT? Several measures indicated that subjects indeed showed recovery of executive functioning. In the larger research project on the therapy protocol (Spikman et al., 2009) the total group of patients showed most improvement in daily life executive functioning, measured with questionnaires and tests, at T2. Moreover, patients included in the experimental treatment group, the same treatment subjects B-F had received, performed better on the Executive Secretariat Task than the patients who had received the control treatment. In the neuroimaging study, four of the five subjects who received CRT performed best in daily life at T2. At that time, daily life was reported to have changed most towards what it used to be before stroke and the goals subjects had formulated for themselves had been achieved. Subjects A and E performed best on the Executive Secretariat Task, suggesting they would have the least problems with executive functioning in daily life compared to the other subjects. Indeed, subject E reports the least problems in daily life on the DEX, but subject A reports the second most problems at T2. Going into the DEX-scores deeper we see that in most cases either at T1 or T2 an increase of EF problems in daily life is reported. This seems to contradict the findings on the other measures which suggest that at those points in time most subjects have become more active in daily life and have achieved their

treatment goals. However, considering that one of the main objectives of the CRT protocol is to make subjects and their partners more aware of what EF problems are, these findings are a lot less contradicting. Problems that previously might have gone unnoticed or labelled as something else are now being reported. Another explanation is that, as CRT leads the subjects to become more active in daily life they are confronted more often with their limitations than when they would have stayed at the same level of inactivity as before CRT.

Linking fMRI data to these results on, partly subjective, EF measures provides us with further evidence for the compensatory role of the parietal lobe discussed above. As the results of the DLP were ambiguous we will concentrate on the findings during the ToL. Three of the five patients who completed CRT showed increased parietal activation at T1. In subject B parietal activation decreased at that measurement. Furthermore, subject B reported an increase of executive functioning problems at T1 and he was the only one who reported goals were only slightly reached whereas the others reported more success. These findings support the hypothesis that compensatory parietal activation leads to better executive functioning. The question remains why he showed a deviating activation pattern. There might be a relation with the fact that he started CRT twenty months post onset unlike the others who all started within one year after stroke. This would lead to the conclusion that CRT should be started shortly following stroke for parietal compensatory activation to play a role. However, as it concerns only this single case, such a conclusion cannot be drawn. Subject E showed no differences in parietal activation between T0 and T1 nor between T1 and T2. He was highly educated and his work had involved a great deal of executive functioning. Probably, his high level of premorbid functioning enabled him to perform the tests in fMRI without extra parietal compensation. Next to B, subject E was the only subject reporting an increase of executive functioning problems in daily life at T1. On the basis of these data it is mere speculation to suggest that they would have experienced fewer problems at T1 had they shown extra parietal activation. The deviating results of subject C at T2 also fit into this parietal compensation hypothesis. At T2 compared to T1, subject C was the only subject showing merely an increase of parietal activation. Furthermore, subject C was the only subject who completed CRT and showed no increases of frontal activation at T2 compared to T1. In his case the increase of parietal activation might have been a reaction to the low level of frontal activation. Regrettably, it seemed that this long after CRT extra parietal activation did not result in better functioning: subject C reported a decrease of daily life activities. There is another plausible and possibly linked explanation for the increased parietal activation besides this compensation hypothesis. Our measures, however, do not allow either confirmation or rejection of it. This explanation lies in the fact that in most previous

studies parietal activation during the ToL has been associated with visuo-spatial information processing. It is well-known that information processing after brain injury is slower and more effortful (e.g. Brouwer, 1985; Gerritsen, Berg, Deelman, Visser-Keizer, & Meyboom-deJong, 2003; Ponsford et al., 2008; Schmitter-Edgecombe, Marks, Fahy, & Long, 1992; Spikman, Zomeren van, & Deelman, 1996). As suggested earlier in this discussion, it is very well possible that processing visuo-spatial information required our subjects to recruit more brain areas and use those areas more intensively. It would be worthwhile to study this option further. The DLP would be an essential test in that research as it does not involve visuo-spatial information processing.

This combination of data also provided insight in the frontal brain processes underlying recovery of executive functioning after CRT. For instance, changes in frontal activation after CRT seem to be linked with resumption of previous activities. At T2 relative to T0, subjects A and C showed the most extensive decrease of frontal activation in comparison to the other subjects. Both subjects were also the only subjects reporting daily life activity level decreased at that time. The findings in subject C were discussed above. Subject A is a totally different story as he decided to stop CRT after a few sessions. In these first sessions information is given about the dysexecutive syndrome and the effect it has on daily life functioning in general. Additionally, subjects are informed about their own cognitive and executive impairments in relation to daily life functioning in order to gain insight into their weaknesses and strengths. These sessions might have provided him with enough knowledge to adjust his daily life in such a way that he could engage in more daily life activities again, which was accompanied by an increase of frontal activation at T1. However, at T2 it became clear that he had not learned the skills to remain active in daily life at that level and that his frontal activation did not improve further: there was a decrease of frontal activation found at T2, even below the level of T0, and he reported a worsening on the Role Resumption List as compared to T1.

Another interesting finding was that three of the five subjects who completed CRT, showed a decrease of frontal activation from T0 to T1 before they showed an increase at T2. This suggests that CRT delayed the increase of frontal activation and made these subjects use their EF even less. Maybe this finding relates to the fact that, although subjects reported to have resumed more activities in daily life, during CRT all these activities were planned together with the therapist and performed as homework assignments. It is not until therapy is completed that subjects independently start using the strategies they learned. This does not explain why the two other subjects did show an increase. Another explanation lies in the specific deficits of the

subjects. The three subjects with decreased frontal activation at T1 all reported problems with regulation of behaviour or emotions, either being too apathetic or too impulsive. The two subjects who showed an increase of frontal activation at T1 had aphasia. As CRT was tailored to the subjects' specific executive and cognitive functioning deficits it is likely that these differences in emphasis within a therapy led to diverse changes in brain activation.

In summary, the results of this study lead to the following conclusions and hypotheses. First, at T0, T1, and T2 patients were less frontally active than healthy controls and compensated through extra parietal activation. Second, the compensatory activation of the parietal lobe might be restricted to the first year after stroke. Third, we found a link between the positive effects of CRT: subjects becoming more active in daily life and increased frontal activation. As expected, CRT did lead to increased frontal activation. However, this process stretched over a longer period of time than expected. The increase of frontal activation seemed dependent on actual application of the learned strategies to daily activities. Fourth, the first few sessions of the evaluated CRT protocol (Spikman et al., 2009) already resulted in better functioning, but more training was needed to remain at or increase that level of functioning at T2. Finally, tailoring CRT to the specific needs of each individual patient seemed to be reflected at the level of brain activation changes.

This study has led to interesting results some of which suggest further research. An interesting subject for research would be to find an explanation for the suggested link on group level at T2 between increased frontal activation, better functioning in daily life, and increased report of EF problems. It has been hypothesised by other authors that increased brain activation reflects increased effort which results in better performance, but more complaints as well (e.g. McAllister et al., 2001; Ricker et al., 2001). We did not have enough evidence in our study to draw that conclusion. Additional measures of effort experienced while performing executive functioning tasks in daily life might have clarified this matter. This information would also have been useful to further understand the increased parietal activation in the brain injured subjects. Furthermore, a remark should be made on the DLP. This test was included as it involved more elements from real planning situations in daily life and therefore was expected to reflect better a subject's improvement on the skills learned in CRT. The DLP was only presented to three patients and group analysis did not result in clear brain activation patterns. Individual analysis of ToL and DLP resulted in more or less the same information. Although the results in this study do not seem to demonstrate a clear additional value of the DLP to a more classical fMRI measure, the results in the group of healthy controls did (Lamberts et al., 2009b) . For instance,

the DLP showed greater involvement of the parietal lobe than the ToL. This finding suggests that the DLP could further clarify the function of the parietal lobe in improvement of executive functioning after CRT. Therefore further research using the DLP in larger patient groups is recommended. It might be that the DLP shows, more than the ToL does, the different routes through which patients with a dysexecutive syndrome try to solve everyday planning problems. Finally, research should be done to test the recommendations for clinical practice derived from our results. The first of those findings to be evaluated is whether CRT indeed should be started within a year after brain-injury. Another recommendation to be studied further, is whether CRT aimed at improvement of executive functioning leads to better or faster recovery if it consists only of a short period of intense training, followed by a longer period in which a patient takes up his own life again, but reports to his therapist on a regular basis.

These remarks and recommendations for clinical practice illustrate the additional value of fMRI measures in research on neuropsychological rehabilitation. It allows us to generate and test hypotheses on more levels than when only neuropsychological test results are being collected. Thus, although clinical use of fMRI in neuropsychological rehabilitation does still seem a long way to go, our suggestions for further research might provide solutions for problems encountered in CRT and might further improve CRT aimed at executive functioning problems.